Remarks

Claims 12, 16-21, 25-28 and 30-43 are pending in the subject application. Applicants note that the Office Action Summary page indicates that claims 22-24 are pending; however, these claims were canceled in the August 19, 2009 Amendment. By this Amendment, Applicants have canceled claim 30 and amended claims 12, 25, 31 and 40. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 12, 16-21, 25-28 and 31-43 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08, and copies of the references listed herein. Applicants request that the references in the IDS be made of record in the subject application.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 102(b) (over Foresta *et al.* and Acosta *et al.*).

Claims 12 and 31 are objected to because of informalities. The Examiner indicates that the acronym "FSH" should be spelled out for the first instance of use. Applicants gratefully acknowledge the Examiner's careful review of the claims. In accordance with the Examiner's suggestion, claims 12 and 31 have been amended, to recite "follicle stimulating hormone" with the acronym "FSH" in parentheses. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 30 is objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form. By this amendment, Applicants have canceled claim 30. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 40 is objected to because of informalities. Applicants gratefully acknowledge the Examiner's careful review of the claims. Applicants have deleted "15 (currently amended)." at the end of the claim. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 12, 16-28 and 30-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. By this Amendment, Applicants have clarified that claims 12 and 31 are directed to

methods for the reduction or treatment, or reduction and treatment of gamete numerical chromosomal alteration in a male. In addition, there is sufficient antecedent basis for the amended claim 25. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 12, 16-28 and 30-43 are rejected under 35 U.S.C. 112, first paragraph, as not being enabled for the full scope of the claims. Applicants gratefully note that the Office Action acknowledges at page 5 that the specification is enabling for the claimed methods of administering FSH or an FSH variant, wherein said variant is recombinant FSH (rFSH) or CTP-FSH. Applicants respectfully assert that the full scope of the invention is enabled by the as-filed specification.

For an invention to be enabled under the first paragraph of §112, the specification need only teach a person of ordinary skill in the art to make and use the claimed invention. In addition, the requirement for some experimentation and/or screening does not necessarily make a claim non-enabled. "Enablement is not precluded by the necessity for some experimentation such as routine screening. . . A considerable amount of experimentation is permissible, if it is merely routine . . ." (emphasis added). *In re Wands,* 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

Specifically, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. Applicants are not required to disclose every species encompassed by their claims even in an unpredictable art to satisfy the enablement requirement. *In re Angstadt*, 537 F.3d 498, 503 (CCPA 1976). In addition, prophetic examples do not make the disclosure non-enabling. *See Atlas Powder Co. v. E.I. DuPont de Nemous & Co.*, 750 F. 2d 1569, 1577 (Fed. Cir. 1984), *In re Cook*, 439 F.2d 730, 735 (CCPA 1971), MPEP 2164.08.

At the time of the invention, the entire structure of wild-type human FSH, a dimeric hormone consisting of an α subunit and a β subunit, was well known in the art (Schambye *et al.*, WO01/58493 at page 1, lines 9-10; *see* specification at pages 10-11). The α subunit is common to the glycoprotein hormone family, which apart from FSH includes chorionic gonadotropin (CG), thyroid stimulating hormone (TSH), and luteinizing hormone (LH), whereas the β subunit is specific to FSH (Schambye *et al.*, at page 1, lines 10-12). Specifically, the human wildtype α subunit is a 92 amino acid glycoprotein and β subunit is a 111 amino acid glycoprotein; the entire amino acid sequences of both subunits have been identified (Schambye *et al.* at page 1, lines 12-16).

In addition, the structure-function relationship of FSH has been well studied. For instance, Liu *et al.*, J Biol Chem 1993,15; 268 (2): 21613-7, Grossmann *et al.*, Mol Endocrinol 1996 10 (6): 769-79, Roth and Dias (Mol Cell Endocribol 1995 1; 109 (2): 143-9, Valove *et al.*, Endocrinology 1994; 135 (6): 2657-61, Yoo *et al.*, JBiol Chem 1993 25; 268 (18): 13034-42), U.S. Patent No. 5,508,261 and Chappel *et al.*, 1998, Human Reproduction, 13 (3): 18-35 disclose various structure-function relationship studies and identify amino acid residues involved in receptor binding and activation and in dimerization of FSH (Schambye *et al.*, at page 1, lines 26-31).

Given the existing knowledge regarding the structure-function relationship of FSH, it demands no more than ordinary experimentation to determine variants with FSH-activity. For example, Schambye *et al.* disclose polypeptide conjugates exhibiting FSH activity and methods for their preparation and their use in medical treatment (Schambye *et al.* at page 4, lines 26-27). In another example, U.S. Patent No. 5,405,945 discloses producing FSH variants having biological activity of native FSH by modifying the carboxy terminal portion of the CG P subunit or a variant (Schambye *et al.* at page 2, lines 25-33). These variants (having FSH-activity) are further taught in the specification at paragraph 55, see, for example, CTP-FSH and molecules having additional glycosylation sites. In addition, it only takes ordinary experimentation to distinguish variants with FSH-antagonist activity. For example, structures critical for FSH variants with FSH-antagonist activity are discussed in Timossi *et al.* (teaching that "it is well known that deglycosylation of gonadotropins by enzymatic or chemical procedures or by deletion of sites for N-linked glycosylation produces antagonistic analogs"), Barrios-De-Tomasi *et al.* (identifying an isoform of FSH that "exhibited antagonistic effects on FSH action"), and Boime *et al.* (teaching how to make single chain FSH variants with antagonist activities). Thus, one skilled in the art can identify variants with FSH-activity and distinguish them from variants with FSH-antagonistic activity without undue experimentation. In addition, the specification teaches how to use variants with FSH-activity for treating or reducing gamete numerical chromosomal alteration in a male. Accordingly, the full scope of the claims has been enabled and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 12, 16-28 and 30-43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification. Applicants gratefully acknowledge that

the Office Action indicates at page 11 that the specification provides written description for FSH variants such as CTP-FSH or rFSH. The test for sufficiency of the written description is whether the application reasonably conveys to one skilled in the art that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563; MPEP. 2163. The "written description" requirement must be applied in the context of the particular invention and the state of knowledge in the relevant art; it does not require that every invention must be described in the same way. *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). The descriptive text needed to meet these requirements varies with the nature and scope of the claim at issue, and with the scientific and technologic knowledge already in existence.

Furthermore, "a patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed." *Martek Biosciences,* 579 F.3d 1363, 1371 (Fed. Cir. 2009); *see also Bilstad v. Wakalopulos*, 386 F.3d 1116, 23 (Fed. Cir. 2004). Indeed, courts have repeatedly "cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification." *See, e.g., Martek Biosciences,* 579 F.3d 1363, 1371 (Fed. Cir. 2009); *In re Rasmussen,* 650 F.2d 1212, 15 (CCPA, 1981); *Tex. Instruments, Inc. v. Int'l Trade Comm'n*, 805 F.2d 1558, 63 (Fed. Cir. 1986).

One skilled in the art would recognize that Applicants were in possession of the full scope of the claimed genus: FSH variants exhibiting FSH-activity. The breadth of the claimed genus is defined by the distinguishing functional characteristic: exhibiting FSH-activity. The specification provides representative species having the functional characteristic, such as, for example, CTP-FSH and rFSH. The specification also incorporates teachings available in the art regarding structure-function relationship of FSH and the structure critical for preserving FSH-activity (specification at paragraph 55). One example is the published patent application WO01/58493, describing amino acid residues critical for FSH-activity (Schambye *et al.* at page 1, lines 26-30; *see also* Liu *et al.*, J Biol Chem 1993,15; 268 (2): 21613-7, Grossmann *et al.*, Mol Endocrinol 1996 10 (6): 769-79, Roth and Dias (Mol Cell Endocribol 1995 1; 109 (2): 143-9, Valove *et al.*, Endocrinology 1994; 135 (6): 2657-61, Yoo *et al.*, JBiol Chem 1993 25; 268 (18): 13034-42), U.S. Patent No. 5,508,261 and Chappel *et al.*, 1998, Human Reproduction, 13 (3): 18-35 disclosing various structure-function

relationship studies and identifying amino acid residues involved in receptor binding and activation and in dimerization of FSH). Thus, the distinguishing functional characteristic, that is, exhibiting FSH-activity, reasonably conveys to one skilled in the art the corresponding structure of the claimed genus since the structure-function relationship of FSH and amino acid residues critical for FSH-activity were known in the art at the time this application was filed.

Applicants also note that FSH variants recited in the present claims are readily distinguishable from the rejected claim elements in *Regents v. Lilly, Fiers v. Revel, Amgen*, or *Enzo Biochem*, which all involve unknown structures (*see* Office Action at page 10, citing *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd*, 18 USPQ2d at 1016, where the court reasoned that when the invention involves entirely unknown compounds, disclosing "the compound itself is required."). In contrast, structure critical for FSH-activity and structure/function correlation for FSH-activity were known. Thus, facts of this case are similar to the *Capon* case, where the Federal Circuit held that the recitation of the nucleotide sequence of claimed DNA is not required, when the sequence is already known in the field. *Capon v. Eshhar*, 418 F.3d at 1357. A skilled artisan can recognize the corresponding structure of FSH-variants based on known structure-function relationship of FSH, and capable of envisioning the full scope of the claimed genus. Accordingly, the written description requirement is satisfied and reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 12, 16, 17, 19-27, 30-33, 35-39 and 41-43 are rejected under 35 U.S.C. § 102(b) as anticipated by Acosta *et al.* (1991) as evidenced by Moeman *et al.* (2008). The Office Action claims that Moeman *et al.* provide evidence that males with oligoasthenoteratozoospermia have a higher incidence of "XX disomy" as well as aneuploidy and diploidy. Applicants respectfully assert that the references do not anticipate the claimed invention because Acosta *et al.* do not disclose, either expressly or under the principles of inherency, the claim element that the administration of FSH reduces or treats the rate of gamete numerical chromosomal alteration in a male.

It is well settled that in order for the Patent Office to establish a *prima facie* case of anticipation, each and every element of the claimed invention, arranged as required by the claim, must be found in a single prior art reference, either expressly or under the principles of inherency. *See generally In re Schreiber*, 128 F.3d 1473, 1477; *Diversitech Corp. v. Century Steps, Inc.*, 850

F.2d 675, 677-78 (Fed. Cir. 1988); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick*, 730 F.2d 1452, 1458 (Fed. Cir. 1984). Additionally, the Patent Office cannot establish inherency merely by demonstrating that the asserted limitation is probable or possible. *In re Oerlich*, 666 F.2d 578, 581 (C.C.P.A. 1981). "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Scaltech Inc. v. Retec/Tetra, L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999). *See also Cont'l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) ("When the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference.").

In this case, the claims require diagnosing a male as having XX disomy or YY disomy and administration of FSH for reducing or treating the rate of gamete numerical chromosomal alteration in a male. The Acosta *et al.* reference does not indicate that administration of FSH to male patients nor does it appear to teach diagnosing a male with XX or YY disomy or diagnosing a male with gamete numerical chromosomal alterations. The Office Action, recognizing this gap in the teachings of Acosta *et al.*, seeks to the remedy the missing descriptive matter with teachings of Moeman *et al.*, in an effort to demonstrate that male patients with semen parameters, such as poor sperm morphology, concentration and motility, would necessarily have gamete numerical chromosomal alteration (*i.e.*, XX, XY or YY disomy).

Applicants respectfully submit that Moemen *et al.* fail to "make clear that the missing descriptive matter is necessarily present in the thing described in the reference" as required under *Cont'l Can Co. USA, Inc. v. Monsanto Co.* Moemen *et al.* simply studied the mean percentage of gamete chromosomal alteration in 30 idiopathic severe oligoasthenoteratozoospermia (iOAT) males and 20 healthy controls (Moemen *et al.* at page 383, left column, paragraph 2), and found that the mean percentages of XX and XY disomy are 0.18% and 0.37% in iOAT males, as compared to 0.1% and 0.17% in healthy controls (Moemen *et al.* at page 384, left column, paragraph 1); while there is nonsignificant differences in the mean percentage of YY disomy compared to controls (0.09 in iOAT patients versus 0.11%). Thus, a mere presentation of mean percentage or mean frequency does not make clear whether any of individual patients in Acosta *et al.* would necessarily have gamete

numerical chromosomal alteration (*i.e.*, XX, XY or YY disomy) nor does it provide evidence that the treated individuals were diagnosed with XX or YY disomy. In fact, teachings in Moemen *et al.* indicate that semen quality does not universally equate gamete chromosomal alteration in individuals (teaching that "although analysis of semen parameters could provide some indication of function of the testis and spermatozoa, it does not provide information on the condition of the male genome contained in sperm heads" (Moemen *et al.* at page 381, right column, paragraph 2) and that Jakab *et al.* (2003) indicated that the classical parameters of semen analysis (sperm count and motility) did not correlate with the frequency of numerical chromosomal anomalies" (Moemen *et al.* at page 384, right column, paragraph 1)). Therefore, Applicants respectfully assert that Acosta *et al.* do not teach the claim element that FSH reduces or treats gamete numerical chromosomal alteration, and the inherency of this missing element cannot be established by Moemen *et al.* Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Claims 18 and 34 are rejected under 35 U.S.C. § 103(a) as obvious over Acosta *et al.* (1991) and further in view of Loumaye *et al.* (1995). Applicants respectfully assert that a *prima facie* case of obviousness has not been established because the cited references in combination fail to teach the claim element that the administration of FSH reduces or treats the rate of gamete numerical chromosomal alteration in a male.

Establishing a *prima facie* case of obviousness requires the prior art to teach or suggest each and every the claim element. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974). As noted above, Acosta *et al.* fail to teach, either expressly or under the principles of inherency, the claim element that the administration of FSH reduces or treats the rate of gamete numerical chromosomal alteration. The Loumaye *et al.* reference, which teaches that production and pharmacokinetic characteristics of uFSH and rFSH, does not cure the defect of Acosta *et al.* Additionally, Loumaye *et al.* also fail to teach the diagnosis of gamete numerical chromosomal alterations in males. Thus, it is respectfully submitted that the cited combination of references fails to render the claimed invention *prima facie* obvious because each of the limitations of the claimed invention are not taught and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 28 and 40 are rejected under 35 U.S.C. § 103(a) as obvious over Acosta *et al.* (1991) and further in view of Bouloux *et al.* (2001). Applicants respectfully assert that a *prima facie* case of obviousness has not been established because the cited references in combination fail to teach every claim element. As noted above, Acosta *et al.* fail to teach, either expressly or under the principles of inherency, the claim element that the administration of FSH reduces or treats the rate of gamete numerical chromosomal alteration. The Bouloux *et al.* reference, which teaches that CTP-FSH could lead to more convenient dosing regimens, does not cure the defect of Acosta *et al.* Thus, it is respectfully submitted that the cited combination of references fails to render the claimed invention *prima facie* obvious and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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